Two New C_{21} Steroidal Glycosides from the Stems of *Cynanchum paniculatum* KITAG.

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Two new glycosides, (3*β*,8*β*,9*α*,16*α*,17*α*)-14,16*β*:15,20*α*:18,20*β*-triepoxy-16*α*,17*α*-dihydroxy-14-oxo-13,14:14,15-disecopregna-5,13(18)-dien-3-yl *α*-cymaropyranosyl-(1→4)-*α*-digitoxopyranosyl-(1→4)-*α*-oleandropyranoside (**1**) and (3*β*,8*β*,9*α*,16*α*,17*α*)-14,16*β*:15,20*α*:18,20*β*-triepoxy-16*β*:17*α*-dihydroxy-14-oxo-13,14:14,15-disecopregna-5,13(18)-dien-3-yl *α*-oleandropyranosyl-(1→4)-*α*-digitoxopyranosyl-(1→4)-*α*-oleandropyranoside (**2**) were isolated from the stems of *Cynanchum paniculatum* (BUNGE) KITAG. The structures of the new compounds were elucidated by means of spectral data, including HR-ESI-MS, and 1D-, and 2D-NMR.

Introduction. – *Cynanchum paniculatum* (BUNGE) KITAG. (Asclepiadaceae), a traditional Chinese medicine distributed extensively in China, has been used mainly as an anodyne for the treatment of snake bites, hives, and chronic tracheitis [1]. Previous studies showed that the major components of *Cynanchum paniculatum* were paeonol [2] and steroidal glycosides [3]. In particular, there were steroidal glycosides with a 13,14:14,15-disecopregnane-type aglycone. To date, more than 30 glycosides of this type have been identified in *Cynanchum paniculatum*. Further investigation on *C. paniculatum* revealed two new glycosides with the same aglycone from this medicinal plant. The new compounds were determined to be (3*β*,8*β*,9*α*,16*α*,17*α*)-14,16*β*:15,20*α*:18,20*β*-triepoxy-16*α*,17*α*-dihydroxy-14-oxo-13,14:14,15-disecopregna-5,13(18)-dien-3-yl *α*-cymaropyranosyl-(1→4)-*α*-digitoxopyranosyl-(1→4)-*α*-oleandropyranoside (**1**) and (3*β*,8*β*,9*α*,16*α*,17*α*)-14,16*β*:15,20*α*:18,20*β*-triepoxy-16*β*:17*α*-dihydroxy-14-oxo-13,14:14,15-disecopregna-5,13(18)-dien-3-yl *α*-oleandropyranosyl-(1→4)-*α*-digitoxopyranosyl-(1→4)-*α*-oleandropyranoside (**2**). The present work describes the isolation and structural elucidation of those two new C_{21} steroidal glycosides.

Results and Discussion. – Compound **1** was obtained as a colorless, amorphous solid. The IR spectrum revealed the presence of OH groups (3494 cm^{-1}), C=C bonds (1656 cm^{-1}), and C=O groups (1728 cm^{-1}). The specific rotation $[\alpha]_D^{25}$ ($c = 0.04$, MeOH) was +47.1. The molecular formula was established as $C_{41}H_{62}O_{15}$ by HR-ESI-MS, showing the $[M+Na]^+$ ion peak at m/z 817.4000 ($C_{41}H_{62}NaO_{15}^+$, calc. 817.3981). Two Me groups at δ(H) 0.91 (*s*) and 1.47 (*s*) were observed in the ^{1}H-NMR spectrum (*Table 1*). The ^{13}C-NMR spectra showed a CO C-atom signal (δ(C) 178.5 (*s*, C(14)) and four unsaturated ^{13}C signals (δ(C) 140.5 (*s*, C(5)); 119.9 (*d*, C(6)); 116.4 (*s*, C(13));

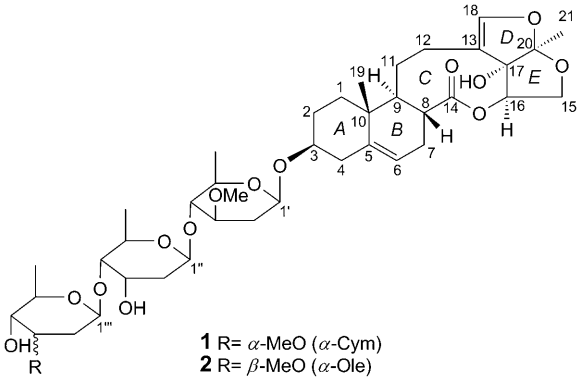

Table 1. *^{1}H- and ^{13}C-NMR Data of Compound* **1**. δ in ppm, J in Hz.

	δ(C)[a])	δ(H)[b])		δ(C)[a])	δ(H)[b])
H_α–C(1)	36.5 (*t*)	1.05–1.08 (*m*)	Oleandropyranose:		
H_β–C(1)		1.94–1.96 (*m*)	H–C(1′)	97.9 (*d*)	4.52 (*dd*, *J* = 10.0, 2.0)
H_α–C(2)	29.4 (*t*)	1.21–1.23 (*m*)	H_α–C(2′)	36.7 (*t*)	2.20–2.22 (*m*)
H_β–C(2)		1.53–1.54 (*m*)	H_β–C(2′)		1.47–1.53 (*m*)
H–C(3)	77.8 (*d*)	3.52–3.56 (*m*)	H–C(3′)	79.2 (*d*)	3.31–3.34 (*m*)
H_α–C(4)	38.7 (*t*)	2.31–2.35 (*m*)	H–C(4′)	82.6 (*d*)	3.16–3.19 (*m*)
H_β–C(4)		2.16–2.19 (*m*)	H–C(5′)	71.2 (*d*)	3.22–3.25 (*m*)
H_β–C(5)	140.5 (*s*)		Me(6′)	18.3 (*q*)	1.26 (*d*, *J* = 6.5)
H–C(6)	119.9 (*d*)	5.39 (*t*-like)	MeO	56.6 (*q*)	3.41 (*s*)
H_α–C(7)	27.7 (*t*)	2.06–2.08 (*m*)	Digitoxopyranose:		
H_β–C(7)		2.42–2.45 (*m*)	H–C(1″)	98.6 (*d*)	5.00 (*dd*, *J* = 10.0, 2.0)
H–C(8)	53.2 (*d*)	1.25–1.30 (*m*)	H_α–C(2″)	37.1 (*t*)	2.10–2.13 (*m*)
H–C(9)	40.6 (*d*)	2.46–2.49 (*m*)	H_β–C(2″)		1.70–1.72 (*m*)
C(10)	38.6 (*s*)		H–C(3″)	67.7 (*d*)	4.05–4.06 (*m*)
H_α–C(11)	20.6 (*t*)	1.33–1.36 (*m*)	H–C(4″)	79.5 (*d*)	3.19–3.22 (*m*)
H_β–C(11)		2.48–2.51 (*m*)	H–C(5″)	68.7 (*d*)	3.74–3.78 (*m*)
H_a–C(12)	29.4 (*t*)	2.10–2.12 (*m*)	Me(6″)	18.2 (*q*)	1.24 (*d*, *J* = 6.5)
H_b–C(12)		1.98–1.99 (*m*)	Cymaropyranose:		
C(13)	116.4 (*s*)		H–C(1‴)	97.4 (*d*)	4.90 (*d*-like, *J* = 3.3)
C(14)	178.5 (*s*)		H_α–C(2‴)	30.9 (*t*)	2.28–2.31 (*m*)
H_α–C(15)	66.5 (*t*)	4.14–4.17 (*m*)	H_β–C(2‴)		1.68–1.72 (*m*)
H_β–C(15)		3.81–3.84 (*m*)	H–C(3‴)	75.1 (*d*)	3.60–3.64 (*m*)
H–C(16)	83.1 (*d*)	5.36 (*dd*, *J* = 10.5, 7.0)	H–C(4‴)	72.1 (*d*)	3.21–3.23 (*m*)
C(17)	91.3 (*s*)		H–C(5‴)	65.9 (*d*)	3.80–3.84 (*m*)
H–C(18)	145.7 (*d*)	6.38 (*s*)	Me(6‴)	17.9 (*q*)	1.29 (*d*, *J* = 6.5)
Me(19)	17.9 (*q*)	0.91 (*s*)	MeO	56.3 (*q*)	3.40 (*s*)
C(20)	119.6 (*s*)				
Me(21)	19.9 (*q*)	1.47 (*s*)			
HO–C(17)		4.13 (br. *s*)			

[a]) Measured at 125 MHz in $CDCl_3$. [b]) Measured at 500 MHz in $CDCl_3$.

(145.7 (*d*, C(18)); *Table 1*). The data of the ^{13}C-NMR and the DEPT spectra indicated a 15,20 : 18,20-diepoxy-13,14 : 14,15-disecopregnane-type skeleton as the aglycone moiety [4][5]. The CH signal at δ(C) 77.8 (*d*), together with the COSY correlation H−C(3)/H$_\beta$−C(4) and the HMBC correlation H$_\beta$−C(4)/C(6) enabled the location of an O-atom at C(3). The quarternary C-atom at δ(C) 91.3 (*s*), combined with HMBC correlations C(20)/HO−C(17), C(17)/H−C(18), H−C(16), and H−C(21) revealed the presence of a OH group at C(17). In addition, the HSQC and HMBC spectra (*Fig. 1*) provided solid evidence to unambiguously assign all signals of the aglycone of **1** as shown in *Table 1*. The ROESY correlations of H−C(3)/H$_\alpha$−C(4), H$_\alpha$−C(4)/H$_\alpha$−C(7), H$_\alpha$−C(7)/H−C(9), H$_\beta$−C(7)/H−C(8), and H$_\beta$−C(7)/Me(19) indicate that the orientations of H−C(3), H−C(8), and H−C(9) were α, β, and α, respectively. Moreover, the ^{1}H-, ^{13}C-NMR data of the rings *D* and *E* were similar to those of hancopregnane isolated from *Cynanchum hancockianum* [5]. Consequently, the orientations of H−C(16), HO−C(17) and Me−C(20) were confirmed to be α, α, and α. Therefore, the structure of the aglycone of **1** was determined as neocynapanogenin F [6].

The ^{1}H- and ^{13}C-NMR spectroscopic data of the sugar moiety of **1** (*Table 1*) exhibited three Me groups (δ(H) 1.26 (*d*, *J* = 6.5), 1.24 (*d*, *J* = 6.5), and 1.29 (*d*, *J* =

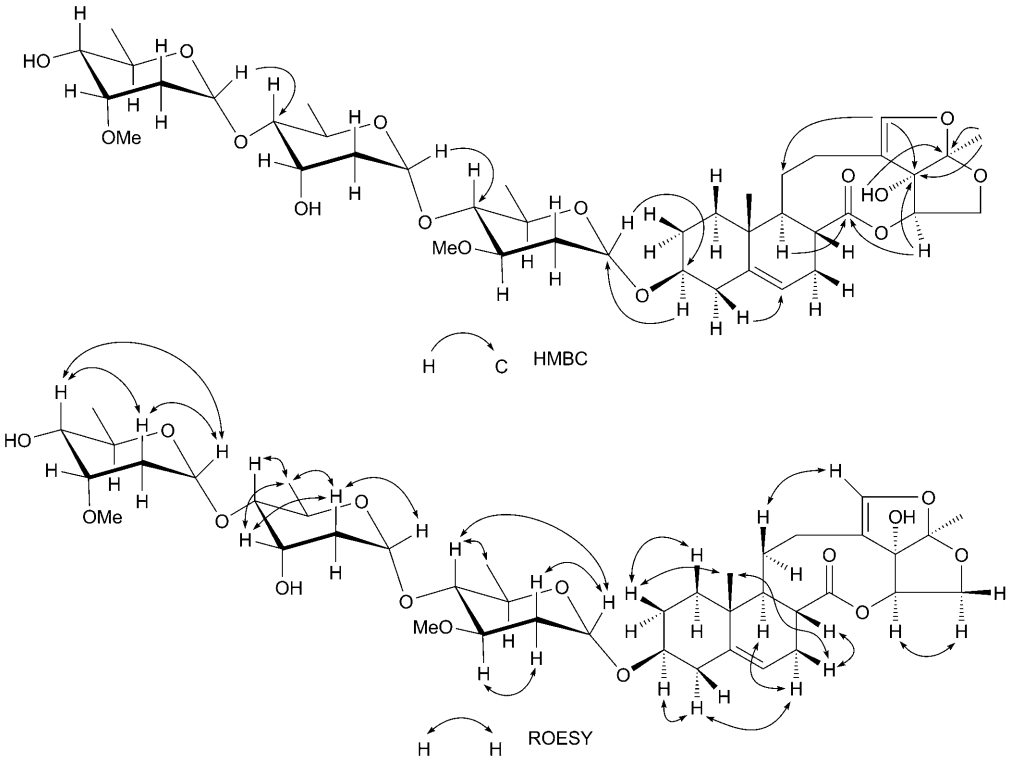

Fig. 1. *Key HMBC and ROESY correlations for* **1**

6.5)), two MeO groups (δ(H) 3.41 (*s*), 3.40 (*s*)) and three CH_2 groups (δ(C) 36.7, $\delta(H_\beta)$ 1.47–1.53, $\delta(H_\alpha)$ 2.20–2.22 ($CH_2(2')$); δ(C) 37.1, $\delta(H_\beta)$ 1.70–1.72, $\delta(H_\alpha)$ 2.10–2.13 ($CH_2(2'')$); and δ(C) 30.9, $\delta(H_\beta)$ 1.68–1.72, $\delta(H_\alpha)$ 2.28–2.30 ($CH_2(2''')$)) as well as three anomeric H-atoms (δ(H) 4.52 (*dd*, $J = 10.0, 2.0$), 5.00 (*dd*, $J = 10.0, 2.0$), and 4.90 (*d*-like, $J = 3.3$)), which, combined with the ^{1}H,^{1}H-COSY and HSQC spectra, suggested the presence of three 2,6-dideoxy sugars (*Fig. 1*). They were identified as α-oleandropyranose, α-digitoxopyranose, and α-cymaropyranose by the ^{13}C-NMR spectroscopic data of the three anomeric C-atoms (δ(C) 97.9 (*d*), 98.6 (*d*), and 97.4 (*d*)), and the coupling constants in the ^{1}H-NMR spectra as well as the NOEs in the ROESY spectra. The correlations within the sugar moieties H–C(1′)/H–C(4′), H–C(4′)/Me(6′), H_α–C(2′)/H–C(3′), H–C(1″)/H_β–C(2″), H–C(3″)/Me(6″), Me(6″)/H–C(4″), and H–C(1‴)/H–C(4‴) in the ROESY spectrum (*Fig. 1*) further confirmed the structures of the individual sugars. The HMBC correlations of H–C(1″)/C(4′) and H–C(1‴)/C(4″) (*Fig. 1*) revealed a linear linkage of the sugar chain. The ^{1}H- and ^{13}C-NMR data of the sugar moiety were similar to those of cynatroside A isolated from *Cynanchum atratum* [7]. The linking position of the sugar moiety at C(3) was deduced from the HMBC correlation H–C(1′)/C(3). Therefore, the structure of compound **1** was unequivocally assigned as (3β,8β,9α,16α,17α)-14,16β:15,20α:18,20β-triepoxy-16α,17α-dihydroxy-14-oxo-13,14:14,15-disecopregna-5,13(18)-dien-3-yl α-cymaropyranosyl-(1 → 4)-α-digitoxopyranosyl-(1 → 4)-α-oleandropyranoside.

Compound **2** was obtained as a colorless, amorphous solid. The IR spectrum revealed the presence of OH groups (3463 cm^{-1}), a C=C bond (1655 cm^{-1}), and a C=O group (1727 cm^{-1}). The specific rotation $[\alpha]_D^{25}$ ($c = 0.28$M, MeOH) of compound **2** was determined to be +28.4. The molecular formula was established by HR-ESI-MS as $C_{41}H_{62}O_{15}$ from the $[M+Na]^+$ ion peak at *m*/*z* 817.3949 ($C_{41}H_{62}NaO_{15}^+$, calc. 817.3981). Compared to compound **1**, the ^{13}C-NMR spectroscopic data were similar, with a difference of five ^{13}C signals of the terminal sugar. The ROESY correlations of H–C(1‴)/H_β–C(2‴), H_α–C(2‴)/H–C(3‴), H_α–C(2‴)/H–C(5‴) and H–C(4‴)/Me(6‴) (*Fig. 2*) revealed that the orientation of H–C(3‴) was different from Me(6‴). Thus, the sugar was identified as α-oleandropyranose. A linear linkage of the sugar chain was also confirmed by the HMBC relationships H–C(1″)/C(4′), and H–C(1‴)/C(4″) (*Fig. 2*). The complete assignment of the sugar resonances was based on the data of cynatratoside C reported from *Vincetoxicum hirundinaria* [8]. The HMBC H–C(1′)/C(3) indicated the linking position of the sugar moiety at C(3). Thus, the structure of compound **2** was identified as (3β,8β,9α,16α,17α)-14,16β:15,20α:18,20β-triepoxy-16β:17α-dihydroxy-14-oxo-13,14:14,15-disecopregna-5,13(18)-dien-3-yl α-oleandropyranosyl-(1 → 4)-α-digitoxopyranosyl-(1 → 4)-α-oleandropyranoside.

Experimental Part

General. TLC: precoated SiO_2 *G* plates (*Qingdao Marine Chemical Plant*, Qingdao, P. R. China). Column chromatography (CC): Silica gel (SiO_2; 200–300 mesh; *Qingdao Marine Chemical Plant*, Qingdao, P. R. China), *Sephadex LH-20* (*GE Healthcare Bio-Sciences AB*, USA), *YMC*GEL ODS-A rp-filler* (500 mesh, *YMC Co., LTD*, Japan). Optical rotation: *RUDOLPH Automatic Polarimeter.* IR Spectra (KBr): *Bruker v33 Spectrometer*; in cm^{-1}. ^{1}H-, ^{13}C-, and 2D-NMR Spectra: *Bruker AV-500* spectrometer and *Bruker AV-300* spectrometer (δ in ppm rel. to Me_4Si, *J* in Hz). MS: *Agilent 1100-JC/MSD-Trap* (ESI-MS) and *Micro-Q-TOF* (HR-ESI-MS) spectrometer.

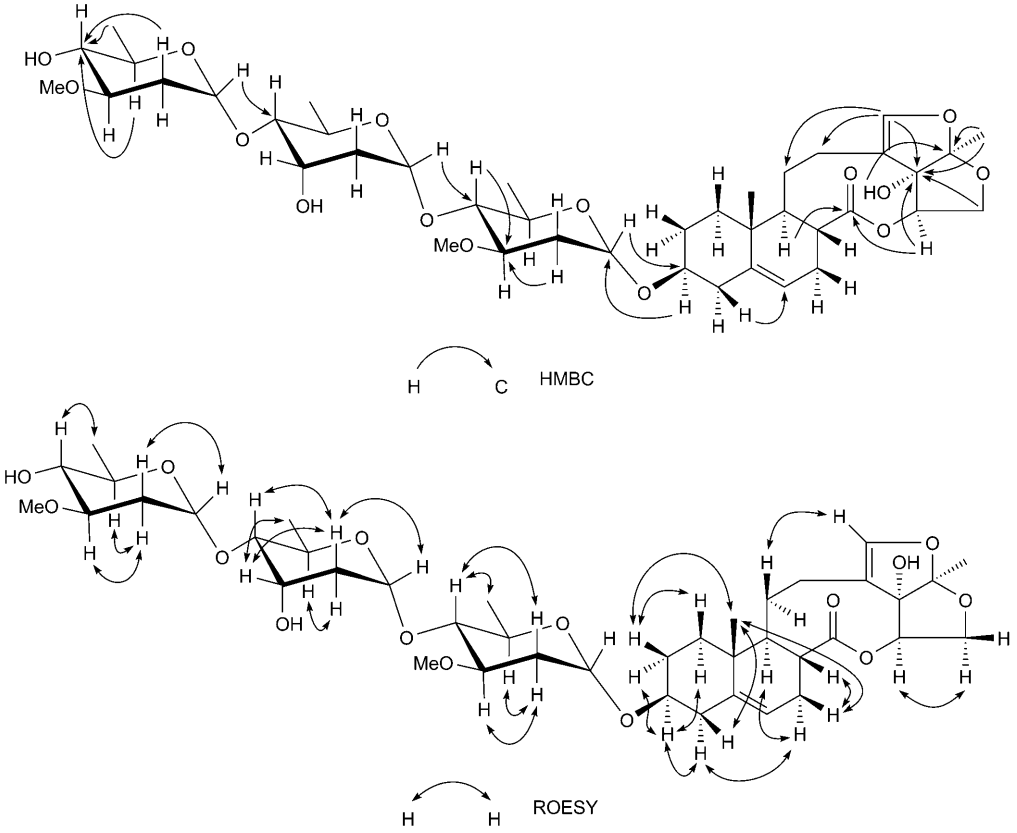

Fig. 2. *Key HMBC and ROESY correlations for* **2**

Plant Material. The stems of *Cynanchum paniculatum* were purchased from *Anhui Fengyuan Pharmaceutical Co., Ltd.*, P. R. China in June 2006, and identified by Prof. *De-Kang Wu* (Nanjing University of Traditional Chinese Medicine). A voucher specimen has been deposited with the Herbarium of China Pharmaceutical University, Nanjing, P. R. China (reference No. 20060705).

Extraction and Isolation. The dried stems of *Cynanchum paniculatum* (8.0 kg) were extracted with 95% EtOH (90 l total) at r.t. for 3 times within 2 d. The filtered soln. was concentrated *in vacuo* to yield a fluid extract (3.0 kg), which was further extracted with AcOEt (15 l). After concentrating the AcOEt extract *in vacuo*, the residue (150.0 g) was separated by CC (SiO_2; gradient elution of petroleum ether (PE)/acetone 1:1 → acetone) to afford 20 fractions (*Frs. 1.1–1.20*). *Frs. 1.19–1.20* were combined and further purified by SiO_2 CC with PE/$CHCl_3$/MeOH 10:30:1 to yield seven fractions (*Fr. 2.1–2.7*). *Frs. 2.3–2.5* were combined and further purified by CC (SiO; $CHCl_3$/AcOEt 1:2) to yield two fractions (*Frs. 3.1* and *3.2*). *Fr. 3.2* was subjected to additional CC of *Sephadex* LH-20 with acetone, SiO_2 with PE/$CHCl_3$/MeOH 5:15:0.5 elution and octadecyl silica eluting with MeOH/H_2O 1:1 to afford compounds **1** (18 mg) and **2** (17 mg).

(3β,8β,9α,16α,17α)-14,16β:15,20α:18,20β-Triepoxy-16α,17α-dihydroxy-14-oxo-13,14:14,15-diseco-pregna-5,13(18)-dien-3-yl α-Cymaropyranosyl-(1 → 4)-α-digitoxopyranosyl-(1 → 4)-α-oleandropyrano-side (= *(2a*R,*4a*R,*6a*R,*10*S,*12a*R,*14b*S*)-2a,4,4a,6a,7,9,10,11,12,12a,12b,13,14,14b-Tetradecahydro-14b-hydroxy-2a,12a-dimethyl-6-oxo-6*H*-2,3,5-trioxapentaleno[1′,6′:5,6,7]cyclonona[1,2-*a*]naphthalen-10-yl 2,6-Dideoxy-3-*O*-methyl-α-D-ribo-hexopyranosyl-(1 → 4)-2,6-dideoxy-α-D-ribo-hexopyranosyl-(1 → 4)-2,6-*

Table 2. *^{1}H- and ^{13}C-NMR Data of Compound* **2**. δ in ppm, J in Hz.

	δ(C)[a]	δ(H)[b]		δ(C)[a]	δ(H)[b]
H_α–C(1)	36.4 (*t*)	1.04–1.07 (*m*)	Oleandropyranose:		
H_β–C(1)		1.92–1.95 (*m*)	H–C(1′)	97.9 (*d*)	4.50 (*dd*, J = 10.0, 2.0)
H_α–C(2)	29.4 (*t*)	1.20–1.23 (*m*)	H_α–C(2′)	36.6 (*t*)	2.19–2.23 (*m*)
H_β–C(2)		1.53–1.55 (*m*)	H_β–C(2′)		1.47–1.53 (*m*)
H_β–C(3)	77.7 (*d*)	3.50–3.53 (*m*)	H–C(3′)	79.1 (*d*)	3.30–3.34 (*m*)
H_α–C(4)	38.6 (*t*)	2.28–2.32 (*m*)	H–C(4′)	82.5 (*d*)	3.16 (*t*-like, J = 9.0)
H_α–C(4)		2.09–2.14 (*m*)	H–C(5′)	71.1 (*d*)	3.25–3.27 (*m*)
H_β–C(5)	140.4 (*s*)		Me(6″)	18.1 (*q*)	1.25 (*d*, J = 6.5)
H–C(6)	119.8 (*d*)	5.35 (*d*-like)	MeO	56.5 (*q*)	3.37 (*s*)
H_α–C(7)	27.6 (*t*)	2.08–2.11 (*m*)	Digitoxopyranose:		
H_β–C(7)		2.40–2.43 (*m*)	H–C(1″)	98.4 (*d*)	5.00 (*dd*, J = 10.0, 2.0)
H–C(8)	53.1 (*d*)	1.20–1.23 (*m*)	H_α–C(2″)	37.5 (*t*)	2.06–2.08 (*m*)
H–C(9)	40.5 (*d*)	2.41–2.43 (*m*)	H_β–C(2″)		1.66–1.67 (*m*)
C(10)	38.5 (*s*)		H–C(3″)	68.3 (*d*)	3.80–3.83 (*m*)
H_α–C(11)	20.5 (*t*)	1.36–1.40 (*m*)	H–C(4″)	81.0 (*d*)	3.23–3.24 (*m*)
H_β–C(11)		2.45–2.48 (*m*)	H–C(5″)	67.8 (*d*)	4.06–4.07 (*m*)
H_a–C(12)	29.4 (*t*)	2.05–2.10 (*m*)	Me(6″)	18.3 (*q*)	1.26 (*d*, J = 6.5)
H_b–C(12)		1.94–1.97 (*m*)	Oleandropyranose:		
C(13)	116.4 (*s*)		H–C(1‴)	99.4 (*d*)	4.99 (*d*-like, J = 2.0)
C(14)	178.3 (*s*)		H_α–C(2‴)	34.1 (*t*)	2.25–2.26 (*m*)
H_α–C(15)	66.4 (*t*)	4.12–4.16 (*m*)	H_β–C(2‴)		1.48–1.53 (*m*)
H_β–C(15)		3.78–3.81 (*m*)	H–C(3‴)	77.9 (*d*)	3.42–3.44 (*m*)
H–C(16)	82.9 (*d*)	5.33 (*dd*, J = 10.0, 7.5)	H–C(4‴)	75.7 (*d*)	3.13 (*t*-like, J = 9.0)
C(17)	91.2 (*s*)		H–C(5‴)	68.6 (*d*)	3.64–3.67 (*m*)
H–C(18)	145.6 (*d*)	6.35 (*s*)	Me(6‴)	17.9 (*q*)	1.24 (*d*, J = 6.0)
Me(19)	17.7 (*q*)	0.89 (*s*)	MeO	56.4 (*q*)	3.37 (*s*)
C(20)	119.5 (*s*)				
Me(21)	19.9 (*q*)	1.43 (*s*)			
HO–C(17)		4.10 (br. *s*)			

[a]) Measured at 125 MHz in $CDCl_3$. [b]) Measured at 500 MHz in $CDCl_3$.

dideoxy-3-O-*methyl*-α-D-arabino-*hexopyranoside*; **1**). Colorless, amorphous solid. $[\alpha]_D^{25} = +47.1$ (c = 0.04, MeOH). IR (KBr): 3494, 2902, 1728, 1656, 1309, 1272. ^{1}H- and ^{13}C-NMR: *Table 1*. The key correlations of HMBC and ROESY are presented in *Fig. 1*. ESI-MS (neg.): 829.7 ($[M+Cl]^-$). HR-ESI-MS (pos.): 817.4000 ($[M+Na]^+$, $C_{41}H_{62}NaO_{15}^+$; calc. 817.3981).

(3β,8β,9α,16α,17α)-14,16β:15,20α:18,20β-Triepoxy-16β:17α-dihydroxy-14-oxo-13,14:14,15-disecopregna-5,13(18)-dien-3-yl α-*Oleandropyranosyl-(1 → 4)-α-digitoxopyranosyl-(1 → 4)-α-oleandropyranoside* (=*(2a*R,*4a*R,*6a*R,*10*S,*12a*R,*12b*S,*14b*S)*-2a,4,4a,6a,7,9,10,11,12,12a,12b,13,14,14b-Tetradecahydro-14b-hydroxy-2a,12a-dimethyl-6-oxo-6*H*-2,3,5-trioxapentaleno[1′,6′:5,6,7]cyclonona[1,2-*a*]naphthalen-10-yl 2,6-Dideoxy-3*-O-*methyl*-α-D-arabino-*hexopyranosyl-(1 → 4)-2,6-dideoxy*-α-D-ribo-*hexopyranosyl-(1 → 4)-2,6-dideoxy-3*-O-*methyl*-α-D-arabino-*hexopyranoside*; **2**). Colorless, amorphous solid. IR (KBr): 3463, 2931, 1727, 1655, 1307, 1063. $[\alpha]_D^{25} = +28.4$ (c = 0.28M, MeOH). ^{1}H- and ^{13}C-NMR: *Table 2*. The key correlations of HMBC and ROESY are presented in *Fig. 2*. ESI-MS (neg.): 829.6 ($[M+Cl]^-$). HR-ESI-MS (pos.): 817.3949 ($[M+Na]^+$, $C_{41}H_{62}NaO_{15}^+$; calc. 817.3981).

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